



## **IX. Tuberous Sclerosis Complex Research Program**

**Vision:** To lessen the impact of tuberous sclerosis.

**Mission:** To encourage innovative research, including natural history studies, aimed at improved prevention, diagnosis, and treatment of tuberous sclerosis complex.

**Congressional Appropriations for Peer Reviewed Research:**

- \$1M in FY02
- \$2M in FY03
- \$3M in FY04

**Funding Summary:**

- 3 FY02 proposals funded
- 4 awards made from the FY03 appropriation
- ~12 awards anticipated from the FY04 appropriation

## supporting natural history studies



**Table IX-1. Funding Summary for the FY03 TSCRP**

Category & Award	Proposals	Awards	Investment <sup>a</sup>
<b>Research</b>			
Idea Development	13	4	\$1.7M
<b>Total</b>	<b>13</b>	<b>4</b>	<b>\$1.7M</b>

<sup>a</sup> \$0.4M was used to partially fund one FY02 award.

## The Disease

Tuberous sclerosis is a genetic disorder that can affect any or all systems of the body. The disorder is characterized by seizures, developmental delays, kidney disease, behavioral problems, and the growth of benign tumors (tubers) on vital organs such as the brain, kidneys, and heart. These tumors typically calcify with age, becoming hard (sclerotic). Children with tuberous sclerosis may have autistic-like symptoms. Tuberous sclerosis affects as many as 25,000 to 50,000 individuals in the United States and about 1 to 2 million individuals worldwide. Although this disorder can be inherited as an autosomal dominant trait, two-thirds of cases are the result of a spontaneous genetic change on one of two genes, *TSC1* or *TSC2*.<sup>1</sup> The *TSC1* gene is located on chromosome 9 and produces the protein hamartin. The *TSC2* gene is located on chromosome 16 and produces the protein tuberlin. Hamartin and tuberlin are believed to act as tumor growth suppressors. Therefore, their dysfunction may underlie the appearance of tumors that characterize tuberous sclerosis. There is currently no cure for this disease; however, surgical intervention and a number of treatments can help affected individuals.

## Program Background

The Department of Defense (DOD) Tuberous Sclerosis Complex Research Program (TSCRP) was established in fiscal year 2002 (FY02) by Joint Appropriations Conference Committee Report No. 107-350, which provided \$1 million (M) for tuberous sclerosis research. The TSCRP has managed \$6M through FY04 to fund peer reviewed tuberous sclerosis research. Seven awards have been made through FY03 in an effort to lessen the impact of this genetic disorder. Appendix B, Table B-7, summarizes the congressional appropriations and the investment strategy executed by the TSCRP for FY03–04.

## The Fiscal Year 2003 Program

Congress appropriated \$2M to continue the TSCRP in FY03. The Idea Development Award that was launched in the first year of the program was again offered to support innovative research aimed at understanding the role and function of proteins produced by the *TSC1* and *TSC2* tumor suppressor genes. A total of 13 proposals were received, and 4 awards were made. Additionally, one FY02 award was partially funded with FY03 TSCRP dollars. Additional summary information about the number of proposals received, number of awards, and dollars invested for the FY03 TSCRP can be found in Table IX-1.

<sup>1</sup> National Institute of Neurological Disorders and Stroke Fact Sheet, 2001; *Harrison's Principles of Internal Medicine*, 15th Edition, McGraw-Hill, 2001.

*“The efforts of this wonderful program will greatly improve the lives of all those affected by tuberous sclerosis complex.”*

*Celia Mastbaum, FY02-04 TSCRP Consumer Peer Review Panel Member*

## The Vision for the Fiscal Year 2004 Program

The TSCRP was continued through an FY04 congressional appropriation of \$3M. Three award mechanisms were offered, one of which was previously established by the TSCRP (Idea Development Awards) and two that are new to the program in FY04 (Concept Awards and Natural History Development Awards). Concept Awards were designed to encourage investigators to boldly explore innovative research directed toward improved prevention, diagnosis, and/or treatment of tuberous sclerosis. Natural History Development Awards were established to fund the development of a multi-institutional natural history study of tuberous sclerosis. Read more about this new award mechanism in the box story on page IX-5. A total of 40 proposals was received, as shown in Table IX-2, and approximately 12 awards are expected.

## Scientific Outcomes and Advances

While the first six awards to TSCRP investigators were made in FY02, TSCRP-funded research presents promise for the future. The following projects represent some of the achievements made by TSCRP-supported investigators to lessen the impact of this genetic disorder.

### Elucidating the Functions of the TSC1 and TSC2 Genes

*Elizabeth Henske, M.D., Fox Chase Cancer Center, Philadelphia*

Tuberous sclerosis is an inherited disease caused by mutations in the *TSC1* or *TSC2* genes. Approximately 80% of people with tuberous sclerosis suffer from epileptic seizures, which are often resistant to anticonvulsive therapy. Other manifestations of the disorder, including kidney disease and tumors on vital organs, also can be severe, yet there are no treatments specific to tuberous sclerosis. A complete understanding of the functions of the TSC1 protein, hamartin, and the TSC2 protein, tuberin, is required for the development of targeted therapeutics. Dr. Elizabeth Henske, a recipient of an FY02 Idea Development Award, is investigating hamartin and tuberin function in the yeast *Schizosaccharomyces*

**Table IX-2. Award Mechanisms Offered and Proposals Received for the FY04 TSCRP**

Category & Award	Proposals
<b>Research</b>	
Concept	26
Idea Development	13
<b>Research</b>	
Natural History Development Awards	1
<b>Total</b>	<b>40</b>

*pombe*. Yeast model systems provide powerful and convenient means to examine important cellular and molecular processes, as many pathways are similar in yeast and mammals and experiments can be performed more rapidly than in mice or other mammalian systems. Dr. Henske determined that the loss of either *TSC1* or *TSC2* in yeast resulted in decreased uptake of arginine, an amino acid used for the synthesis of proteins, polyamines (molecules required for cell growth), and nitric oxide (a signaling molecule involved in many cellular functions). Expression of putative amino acid and polyamine transporters also was lower in mutant yeast than in normal control yeast. Moreover, deficiency in either *TSC1* or *TSC2* caused decreases in intracellular levels of glutamate and other amino acids. These results indicate that hamartin and tuberin play critical roles in amino acid sensing, uptake, and metabolism and that tuberous sclerosis symptoms may be linked to defects in those key cellular functions. Importantly, diminished glutamate uptake from the synapses in the brains of *TSC1*-deficient mice is believed to contribute to seizure development, suggesting that the yeast model may provide a novel system for the study of tuberous sclerosis-related epilepsy and for preclinical screening of new therapeutics that may ameliorate seizures in individuals with the disease.

*For additional information about this research, please refer to the following publication:*

- Van Slegtenhorst M, Carr E, Stoyanova R, et al. 2004. *Tsc1*<sup>+</sup> and *tsc2*<sup>+</sup> regulate arginine uptake and metabolism in *Schizosaccharomyces pombe*. *Journal of Biological Chemistry* 279:12706–12713.

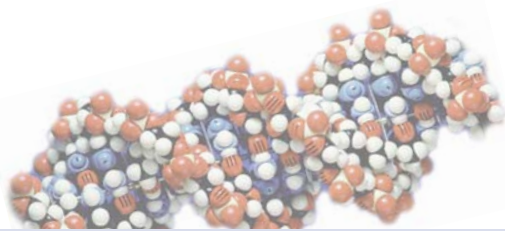
*"The TSCRP has generated great interest and excitement in the research community by providing a new source of funding for TSC research."*

*Vicky Holets Whittemore, Ph.D., FY04 TSCRP IP Chair*

### **Regulation of Angiogenic Proteins by Tuberin**

*William Kaelin, Jr., M.D., Dana-Farber Cancer Institute, Boston*

Tuberous sclerosis, a disorder caused by mutations in the *TSC1* or *TSC2* genes, is characterized by the development of benign tumors. Some patients with tuberous sclerosis also develop renal cell carcinoma and other malignant tumors. Tumor growth depends on the formation of new blood vessels, a process known as angiogenesis. Inhibition of a key angiogenic protein, vascular endothelial growth factor (VEGF), can delay cancer progression in some patients with metastatic renal cell carcinoma. VEGF expression in many tumor types is enhanced by a protein called hypoxia-inducible factor (HIF). Dr. William Kaelin, an investigator at the Dana-Farber Cancer Institute, determined that the TSC2 protein, tuberin, negatively regulates HIF and VEGF through multiple pathways. He also found that the loss of TSC2-enhanced cellular HIF and VEGF levels, particularly under conditions of chronic oxygen deprivation (hypoxia). Dr. Kaelin plans to elucidate the molecular mechanisms by which tuberin regulates HIF with support from an FY03 Idea Development Award. Improved understanding of the role of *TSC2* in controlling angiogenesis may lead to better treatments for renal cell carcinoma and other tumors associated with tuberous sclerosis.



### **Signs and Symptoms**

*Because TSC affects multiple organs, a variety of symptoms may be experienced. The disorder can cause benign tumors, called tubers, to grow in various organs, including the skin, brain, heart, kidneys, lungs, and eyes. However, in most individuals with TSC, only some of these organs are involved, and symptoms vary depending on which organs and systems are affected. In addition to the growth of benign tumors, other signs and symptoms of TSC include seizures, mental disabilities, skin abnormalities, and behavior problems. Some patients with TSC also develop renal cell carcinoma and other malignant tumors.*

### **Bottom Line**

Since FY02, the DOD TSCRP has been responsible for managing \$6M in congressional appropriations, resulting in seven awards through FY03. Projects funded by this newly established program are anticipated to lead to the substantial improvement in the understanding, diagnosis, and treatment of tuberous sclerosis and enhance the quality of life of persons with the disease. Research highlights, award data, and abstracts of funded TSCRP proposals can be viewed on the Congressionally Directed Medical Research Programs website (<http://cdmrp.army.mil>).

### **Fiscal Year 2004**

#### **Integration Panel Members**

**Vicky Holets Whittemore, Ph.D.** (Chair),  
Tuberous Sclerosis Alliance

**Elizabeth Petri Henske, M.D.** (Chair Elect), Fox  
Chase Cancer Center

**Peter Adamson, M.D.**, University of Pennsylvania  
School of Medicine

**Peter Crino, M.D., Ph.D.**, University of  
Pennsylvania School of Medicine

**Robert Finkelstein, Ph.D.**, National Institute of  
Neurological Disorders and Stroke

**Jackson Gibbs, Ph.D.**, Merck Research  
Laboratories

**William Johnson, M.D.**, University of Medicine  
and Dentistry of New Jersey, Robert Wood  
Johnson Medical School

**Bruce Korf, M.D., Ph.D.**, University of Alabama,  
Birmingham

**Eric Legius, M.D., Ph.D.**, Catholic University of  
Leuven, Belgium

**Judy Small, Ph.D.**, The National  
Neurofibromatosis Foundation, Inc.



### **A Closer Look: The Natural History Development Award**

The FY02 and FY03 TSCRP, in accordance with congressional directives, funded innovative research focused on the role and function of the proteins produced by the *TSC1* and *TSC2* genes. The TSC community also has a strong interest in and need for large-scale natural history studies of the disorder in addition to basic research in molecular and cellular biology. Such studies would characterize disease manifestations in each affected organ system and examine the correlations between specific *TSC* gene mutations and symptoms. Lobbying efforts from TSC consumer advocates resulted in the broadening of the FY04 congressional appropriation language to support research aimed at improved prevention, diagnosis, and/or treatment of TSC. To address the needs of individuals with TSC and facilitate the successful implementation of natural history studies, the TSCRP offered a new award mechanism in FY04, the Natural History Development Award. This award, modeled after the NFRP Clinical Trial Development Award, is intended to fund the establishment of the study team, the preparation of a clinical protocol and consent/assent forms, and the development of tools for data collection, analysis, and dissemination. The Natural History Development Award provides a maximum of \$150,000 for an 18-month period, with \$100,000 available at the time of the award and the second installment contingent upon the submission of a natural history study proposal to the TSCRP in FY05. Thus, this award mechanism is intended to elucidate the clinical course of TSC, which may ultimately aid in the prediction of disease prognosis, the development of targeted therapies, and the evaluation of the efficacy of new treatments in clinical trials.

*“I am honored to have been part of the TSCRP as a scientific reviewer.”*

*Kristine S. Vogel, Ph.D.,  
FY02-04 TSCRP Peer Review Panel Member*

